GENERAL GUIDELINES FOR MODIFICATION OF LEUCOVORIN (LV) DOSAGE FOLLOWING HIGH DOSE METHOTREXATE

Time after the START of infusion	Serum creatinine	Methotrexate level	Action
At 24 hrs		If methotrexate is infused *as a short infusion* (over 0.5 – 6 hours), and level GREATER than 5 micromol/L	1) INCREASE LV to 100 mg/m^2 IV Q6H. 2) *Increase fluid intake to 4 – 6 liters per day (LV dosages may be reduced, as indicated, as serum methotrexate level decreases).
At 24 hrs		If methotrexate is given as *continuous infusion for 24 hrs,* and level GREATER than 20 micromol/L at the end of infusion	1) Adjust LV to 50 mg IV/PO Q6H. 2) Increase fluid intake to 4–6 liters per day.
Recommendations BELOW apply to both continuous infusion and short infusion of high dose methotrexate			
At 48 hrs		If LESS than 1 micromol/L	Continue the same dose as initially started.
		If 1 – 5 micromol/L	1) Adjust LV to 50 mg IV/PO Q6H. 2) Increase fluid intake to 4 – 6 liters per day.
		If 5 – 10 micromol/L	1) Adjust LV 100 mg/m^2 IV Q6H (LV dosages may be reduced, as indicated, as serum methotrexate level decreases). 2) Increase fluid intake to 4 – 6 liters per day.
		If 10 – 20 micromol/L	1) Adjust LV to 200 mg/m^2 IV Q6H (LV dosages may be reduced, as indicated, as serum methotrexate level decreases). 2) Increase fluid intake to 4 – 6 liters per day.
		If >20 – 50 micromol/L	1) Adjust LV 500 mg/m^2 IV Q6H (LV dosage may be reduced as indicated, as serum methotrexate level decreases). 2) Increase fluid intake to 4 – 6 liters per day.
At 72 hrs		If methotrexate is given as *continuous infusion,* and level GREATER than 0.1 micromol/L but less than 1 micromol/L at 48 hrs; If methotrexate is given *as a short infusion* (over 0.5–6 hours), and level GREATER than 0.2 micromol/L but less than 1 micromol/L at 48 hrs;	1) Adjust LV to 50 mg IV/PO Q6H until the methotrexate level is less than 0.05 micromol/L. 2) Increase fluid intake to 4 – 6 liters per day.
	If serum creatinine is increased by ≥ 50% from baseline on the next day		1) Adjust LV to 100 mg/m^2 IV Q6Hand continue until MTX level LESS than 0.05 micromol/L (LV dosages may be reduced, as indicated, as serum methotrexate level decreases). 2) Increase fluid intake to 4–6 liters per day.

***Fluid of 2 – 3 liters per day with urinary alkalinization with 50–100 mEq/m^2 per day should be given prior to methotrexate infusion to ensure urine pH is 7 or greater. Hydration should be continued for 24 to 48 hrs after the methotrexate infusion is complete.**

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- Doses of leucovorin greater than 50 mg have to be given as intravenous form due to decreased oral bioavailability of leucovorin at dose >50 mg.
- Monitor for signs/symptoms of increased methotrexate toxicities: nausea/vomiting, mucositis, low urine pH, low urine output, increased serum creatinine, neurotoxicity, and liver toxicities).
- Patients who are at high risk of methotrexate toxicity include those with pre-existing renal dysfunction, prior cisplatin therapy, "third spacing" (pleural effusion, ascites, etc) or GI obstruction.
- Drugs such as aspirin, penicillins, non-steroidal anti-inflammatory drugs, probenecid, sulfamethoxazole/trimethoprim (Bactrim®/Septra®) should be placed on hold during methotrexate infusion and may be resumed when methotrexate level is less than 0.05 micromol/L.

REFERENCES

1. Crom WR, Evans WE. Methotrexate. Chapter 29. Applied Pharmacokinetics. Principles of Therapeutic Drug Monitoring. 3rd edition.
2. Ackland SP, Schilsky RL. High-dose methotrexate: A critical reappraisal. *J Clin Oncol* 1987; 5:2017 - 31.
3. Goldie JH, Price LA, Harrap KR. Methotrexate toxicity: Correlation with duration of administration, plasma levels, dose and excretion pattern. *Eur J Cancer* 1972; 8: 409 - 14.
4. Relling MV, Fairclough D, Ayers D, et al. Patient characteristics associated with high-risk methotrexate concentration and toxicity. *J Clin Oncol* 1994;12:1667 - 72.
5. Evans WE, Crom WR, Abromowitch M, et al. Clinical pharmacodynamics of high-dose methotrexate in acute lymphovytic leukemia. *N Engl J Med* 1986;314:471 - 7.
6. Stoller RG, Hande KR, Jacobs SA, et al. Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. *N Engl J Med* 1977;297:630 - 34.
7. Rosen G, Caparros B, Huvos AG, et al. Preoperative chemotherapy for osteogenic sarcoma: Selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. *Cancer* 1982;49:1221 - 30.
8. Skarin AT, Zuckerman KS, Pitman SW, et al. High dose methotrexate with folinic acid in the treatment of advanced non-Hodgkin lymphoma including CNS involvement. *Blood* 1977;50:1039 - 47.
9. Nixon PF, Bertino JR. Effective absorption and utilization of oral formyltetrahydrofolate in man. *N Engl J Med* 1972;286:175 - 9.
10. Delepine N, Delepine G, Cornille H, et al. Dose escalation with pharmacokinetics monitoring in methotrexate chemotherapy of osteosarcoma. *Anticancer Res* 1995;15:489 - 94.
11. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: an active regimen for aggressive mantle-cell lymphoma. *J Clin Oncol*. 1998;16:3803 - 09.
12. Frei E III, Blum RH, Pitman SW, et al. High dose methotrexate with leucovorin rescue. Rationale and spectrum of antitumor activity. *Am J Med* 1980;68:370 - 6.